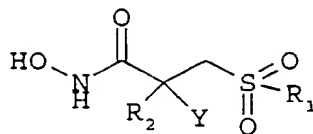


CLAIMS

We claim:

1. A compound of formula I



I

or pharmaceutical acceptable salts thereof wherein:

5 R₁ is

- a) C₄₋₁₂ alkyl,
- b) C₄₋₁₂ alkenyl,
- c) C₄₋₁₂ alkynyl,
- d) -(CH₂)_n-C₃₋₈ cycloalkyl,
- 10 e) -(CH₂)_n-aryl,
- f) -(CH₂)_n-het,

R₂ is

- a) C₁₋₁₂ alkyl,
- b) C₂₋₁₂ alkenyl,
- 15 c) C₂₋₁₂ alkynyl,
- d) -(CH₂)_n-C₃₋₈ cycloalkyl,
- e) -(CH₂)_n-C₃₋₈ cycloalkenyl,
- f) -(CH₂)_n-aryl,
- g) -(CH₂)_n-het,
- 20 h) -(CH₂)_n-Q,

i) -(CH₂)_i-Q or -(CH₂)_i-X-R₄, optionally the -(CH₂)_i- chain can be substituted with one or two C₁₋₄ alkyl or phenyl, which in turn can be substituted with one to three halo or C₁₋₄ alkyl, or

l) -(CH₂)_hCHR₅R₆;

25 R₃ is

- a) H,
- b) C₃₋₆ cycloalkyl,
- c) C₁₋₄ alkyl, or
- d) -(CH₂)_n-phenyl;

X is

- a) -O-,
- b) -S(=O)_j-,
- c) -NR₇-,
- 5 d) -S(=O)₂NR₈-, or
- e) -C(=O)-;

R₄ is

- a) H,
- b) C₁₋₈ alkyl,
- 10 c) -(CH₂)_h-phenyl, or
- d) -(CH₂)_h-het;

R₅ is

- a) C₁₋₄ alkyl, or
- b) -C(=O)R₃;

15 R₆ is

- a) -C(=O)R₃, or
- b) -(CH₂)_hC(=O)R₃;

R₇ is

- a) H,
- 20 b) C₁₋₄ alkyl,
- c) -(CH₂)_h-phenyl,
- d) -C(=O)-R₃,
- e) -S(=O)₂R₃, or
- f) -C(=O)OR₃;

25 R₈ is

- a) C₁₋₄ alkyl, or
- b) -(CH₂)_h-phenyl;

Y is

- a) -OH,
- 30 b) -NR₉R₁₀, or
- c) fluoro;

R₉ and R₁₀ are the same and different and are

- a) H,
- b) -C(=O)-R₃,
- 35 c) -C(=O)-OR₃, or
- d) -C(=O)-NHR₃;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated monomonocyclic or bicyclic heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

- 5 Q is 5- to 10-membered saturated monocyclic or bicyclic heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

aryl, het, C₁₋₁₂ alkyl, C₁₋₄ alkyl C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, -C₃₋₈ cycloalkyl, -C₃₋₈ cycloalkenyl, Q and phenyl being optionally substituted;

h is 0, 1, 2, 3, 4, 5, or 6; i is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; j is 0, 1, or 2; and

- 10 with the following provisos:

a) where R₂ is C₁₋₆ alkyl, Y is other than -NR₉R₁₀,

b) where h is 0, het is attached to the α-position via carbon atom of heterocyclic moiety, and

- c) where h is 0, Q is attached to the α-position via carbon atom of heterocyclic moiety.

2. A compound of formula I according to claim 1 wherein

R₁ is

- a) C₄₋₁₀ alkyl,
 b) -(CH₂)_h-aryl, or
 20 c) -(CH₂)_h-aryl substituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, phenyl, 4-chlorophenyl, O-phenyl, het, O-het, halo, -NO₂, -CF₃, -CN, or -N(C₁₋₄ alkyl)₂;

R₂ is

- a) -(CH₂)_h-Q, or C(CH₃)₂-Q or
 b) -(CH₂)_i-X-R₄, C(CH₃)₂-X-R₄;

25 X is

- a) -S(=O)_j,
 b) -NR₇-;

R₄ is

- a) H,
 30 b) C₁₋₈ alkyl,
 c) -(CH₂)_h-phenyl,
 d) -(CH₂)_h-phenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, phenyl, C₁₋₄ phenoxy, het, halo, -NO₂, or -CN, or
 e) -(CH₂)_h-het;

35 R₇ is

- a) -C(=O)-R₃;

Y is

- a) -OH;

R₃, aryl, het, Q, *h*, *i*, *j* are as defined above, and with the proviso that where *h* is 0, Q is attached to the α-position via carbon atom of heterocyclic moiety.

- 5 3. A compound of formula I according to claim 1 wherein

R₁ is

- a) -(CH₂)_{*h*}-phenyl, or
b) -(CH₂)_{*h*}-phenyl substituted with C₁₋₄ alkoxy, phenyl, 4-chlorophenyl, O-phenyl, O-(pyrid-4-yl) or halo;

10 R₂ is

- a) -(CH₂)_{*i*}-S(=O)₂-R₄, or
b) -(CH₂)_{*i*}-NHR₇;

R₄ is

- a) C₁₋₈ alkyl,
15 b) -(CH₂)_{*h*}-phenyl, or
c) -(CH₂)_{*h*}-phenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, phenyl, C₁₋₄ phenoxy, or halo;

R₇ is

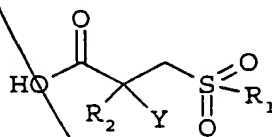
- a) -C(=O)C₁₋₄ alkyl,
20 b) -C(=O)C₃₋₆ cycloalkyl,
c) -C(=O)(CH₂)_{*h*}-phenyl, or
d) -C(=O)-(CH₂)_{*h*}-phenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

Y is

- 25 a) -OH;

and *h* and *i* are as defined above.

4. A compound of formula 8



- 30 or pharmaceutical acceptable salts thereof wherein R₁, R₂ and Y are as defined in claim 1.

5. A compound of claim 1 which is

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-fluorobenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-n-butylbenzenesulfonyl)-propionamide,

5 N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionamide,

10 N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-[N-(cyclopentylcarbonyl)amino]-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide,

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

15 N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)propionamide;

20 N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(methylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

25 N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

30 N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-aminothiazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

35 N-Hydroxy-2-hydroxy-2-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyltetrazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

5 *N*-Hydroxy-2-hydroxy-2-(tetrazol[1,5-b]pyridazin-6-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

10 *N*-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

15 *N*-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-butoxybenzenesulfonyl)propionamide;

20 *N*-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

25 *N*-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

30 *N*-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

35 *N*-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

5 *N*-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

10 *N*-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

15 *N*-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionamide;

20 *N*-Hydroxy-2-hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

25 *N*-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

30 *N*-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide or

35 *N*-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide.

6. A compound of claim 4 which is:

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)-
propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxybenzene-
5 sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)-propionic
acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-
10 propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-propionic
acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenyl-
15 sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenyl-
20 sulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenyl-
sulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-chlorobiphenylsulfonyl)-propionic
acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-
25 propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-
propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzene-
30 sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxy-
benzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxy-
35 benzenesulfonyl)propionic acid;

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Sub B2
2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid

or

5 2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionic acid.

7. A method of inhibiting excess matrix metalloproteinase which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

10 8. A method of claim 7 wherein matrix metalloproteinases comprises stromelysin, collagenase, and gelatinase.

9. A method of treating a human suffering from or susceptible to diseases involving
15 connective tissue degradation which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

10. A method of claim 9 wherein the diseases related to connective tissue degradation are osteoarthritis, rheumatoid arthritis, septic arthritis, and osteopenias such
20 as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, or asthma.

11. The method of claim 7 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

25 12. The method of claim 9 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

13. The method of claim 7 wherein said compound is administered in an amount of
30 from about 0.1 to about 100 mg/kg of body weight/day.

14. The method of claim 9 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

15. A pharmaceutical composition which comprises an amount of the compound of claim 1 effective to inhibit excess matrix metalloproteinases and a pharmaceutically acceptable carrier.

5 16. A compound of claim 1 for use as a medicament.

17. Use of a compound of claim 1 for the manufacture of a medicament for inhibiting excess matrix metalloproteinase in a human suffering from or susceptible to a diseases involving connective tissue degradation.

10

18. The use of claim 17 wherein matrix metalloproteinases comprises collagenases, stromelysins, or gelatinases.

19. The use of claim 17 wherein the disease related to connective tissue
15 degradation is osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, or gastric ulceration.

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